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d/b/a Blue California

UNITED STATES DISTRICT COURT

CENTRAL DISTRICT OF CALIFORNIA

PURECIRCLE USA INC. and PURECIRCLE SDN BHD,

Plaintiffs,

v.

SWEEGEN, INC. and PHYTO TECH CORP. d/b/a BLUE CALIFORNIA,

Defendants.

CASE NO. 8:18-cv-01679-JVS (JDEx)

[Assigned to the Hon. Judge James V. Selna]

DEFENDANTS SWEEGEN, INC. AND PHYTO TECH CORP. D/B/A BLUE CALIFORNIA'S NOTICE OF MOTION AND MOTION OF FOR SUMMARY JUDGMENT ON THE INVALIDITY OF U.S. PATENT NOS. 9,243,273 AND 10,485,257

[Declaration of Dennis Varughese, Statement of Uncontroverted Facts and [Proposed] Order Filed Concurrently Herewith]

Date: April 11, 2022
Time: 1:30 pm

REDACTED VERSION OF DOCUMENT PROPOSED TO BE FILED UNDER SEAL

TO ALL PARTIES AND THEIR ATTORNEYS OF RECORD:

PLEASE TAKE NOTICE THAT on April 11, at 1:30, or as soon as the matter may be heard in the courtroom of the Honorable Judge James V. Selna, defendants SweeGen, Inc. and Phyto Tech Corp. d/b/a Blue California (collectively, "SweeGen") will and hereby do move the court pursuant to Fed. R. Civ. P. 56 for summary judgment as to the invalidity of U.S. Patent Nos. 9,243,273 and 10,485,257 under 35 U.S.C. §§ 101 and 112.

The basis for this Motion is that there is no genuine dispute as to any material fact and that the moving party is entitled to judgment as a matter of law for the following reasons:

1. All claims are invalid under 35 U.S.C. § 101 because they claim a process that occurs naturally in the *Stevia rebaudiana* plant (i.e., a natural phenomenon), which is patent-ineligible subject matter;
2. All claims are invalid under 35 U.S.C § 112 for lack of adequate written description; and
3. All claims are invalid under 35 U.S.C § 112 for lack of enablement.

This Motion is based on this Notice of Motion and Motion, the accompanying Memorandum of Points and Authorities, the Statement of Uncontroverted Facts and Conclusions of Law ("SUF"), the Declaration of Dennies Varughese, and any papers and pleadings on file herewith.

This Motion is made following multiple conferences with counsel, including a conference that took place on January 18, 2022.

Dated: February 14, 2022 Respectfully submitted,

/s/ Karin G. Pagnanelli

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Steviol glycosides are naturally occurring compounds used as low-calorie sweeteners that have long been extracted from the leaves of stevia plants. In those plants, naturally occurring enzymes catalyze reactions in which glucose is added to one type of steviol glycoside to create a different type of steviol glycoside. Plaintiffs (collectively, "PureCircle") have accused Defendants (collectively, "SweeGen") of infringing U.S. Patent Nos. 10,485,257 and 9,243,273, which are directed to the production of steviol glycosides using such enzymes, known as UDP-glucosyltransferases. PureCircle's patent claims seek to monopolize a natural phenomenon: the production of one steviol glycoside from other steviol glycosides using enzymes that occur in nature. After recreating this natural process in one way, PureCircle wrote claims that cover a vast number of similar processes, including processes that use enzymes that have yet to be discovered. SweeGen moves for summary judgement that all the asserted claims are invalid on three independent grounds, each of which is case dispositive: (1) patent-ineligible subject matter; (2) lack of adequate written description; and (3) lack of enablement.

Patent-Ineligible Subject Matter. The claims of the '257 and '273 patents recite processes for making rebaudioside M (*a.k.a.* "Reb M," referred to in the patents as "rebaudioside X") by using any UDP-glucosyltransferase enzyme to add one or more glucose units to other steviol glycosides. No claim requires that these reactions occur in a laboratory setting. No claim specifies the amount of starting material or how long the reactions must take. These claims are therefore broad enough to monopolize the natural activity of UDP-glucosyltransferase enzymes to convert one naturally occurring steviol glycoside to another—a process that occurs naturally within stevia plants. Accordingly, the asserted claims are invalid under 35 U.S.C. § 101 because, *first*, they are directed to ineligible subject matter (*i.e.*, a natural phenomenon). And, *second*, the claims do not recite an "inventive concept" that transforms the nature of the claims into a patent-eligible application. Rather, the claims purport to give PureCircle a monopoly on the natural phenomenon

itself, for the remaining claim elements (*e.g.*, purifying the Reb M produced by the enzyme) represent well-understood, routine, and conventional activity.

Lack of Written Description. Title 35 U.S.C. § 112(a) requires that the patent specification must convey with reasonable clarity to a skilled artisan that, as of the priority date, the inventor was in possession of the full scope of the claimed invention. The purpose of this requirement is to ensure that the scope of the claims does not overreach the scope of the inventor's contribution. Here, the inventors worked with *one* UDP-glucosyltransferase that exists naturally in the stevia plant: the wild type form of the enzyme UGT76G1. The specification does not identify which aspects of the amino acid sequences or three-dimensional structures of this enzyme make it a good catalyst for performing the claimed conversions. Nevertheless, PureCircle's lawyers wrote jarringly overbroad claims that read on *any* UDP-glucosyltransferase capable of performing the claimed conversion.

But enzyme functionality is notoriously unpredictable. Even minor changes to the amino acid sequence of an enzyme can dramatically alter its functionality—including which reactions it can catalyze and whether it can convert steviol glycosides at all. The identification of UDP-glucosyltransferases—and how and why they function the way they do—is ongoing and limited data was available when the patents were filed. It would be necessary to test countless enzymes to figure out which ones are capable of the claimed function. Given that enzyme functionality is unpredictable, the one working example in the specification (which describes using wild-type UGT76G1 enzyme to convert Reb D to Reb M does *not* demonstrate possession of *every possible* UDP-glucosyltransferase that can carry out the conversion for Reb D ('273 patent), much less for *every* steviol glycoside ('257 patent). Therefore, the claims are invalid for lack of written description.

Lack of Enablement. Title 35 U.S.C. § 112(a) contains a related but distinct enablement requirement, which requires that the patent specification be written with sufficient clarity and detail to allow skilled artisans to practice the full scope

of the invention without undue experimentation. Here, however, the breadth of the claims is extreme because they are written in terms of what the enzymes *do*, rather than in terms of their amino acid sequence or physical structure. Making matters worse, the claims cover *any* enzyme, known or unknown, that can add a glucose unit to a steviol glycoside under this functional definition. Small changes in amino-acid sequence can result in large changes in an enzyme's activity, and a given enzyme's activity can be ascertained only by making and testing it. As a result, the quantity of experimentation needed to discover all of the UDP-glucosyltransferases covered by the claims is enormous. Because the skilled artisan would not be able to practice the full scope of these claims without undue experimentation, the claims are invalid for lack of enablement.

I. STATEMENT OF FACTS

The patents-in-suit claim processes for making Reb M, a steviol glycoside used as a natural sweetener. (SUF 5-15, 17.) Steviol glycosides are a class of compounds naturally found in the leaves of *Stevia rebaudiana*, a perennial plant native to South America. (SUF 16.) More than thirty different steviol glycosides have been isolated from stevia leaves. (SUF 19.) Steviol glycosides differ from one another based on the number and location of glucose units attached to the steviol chemical backbone. (SUF 20.) Two locations on the backbone to which glucose units are typically added are the C-13 and C-19 positions. (SUF 21.) "Rebaudiosides" are a subclass of steviol glycosides that have three or more glucose units attached to the steviol backbone. (SUF 22.) Common steviol glycosides that occur naturally in *S. rebaudiana* include stevioside, Reb A, Reb D, Reb E, and Reb M. (SUF 23.)

Naturally occurring steviol glycosides have been used as sweeteners for hundreds of years. (SUF 17-18.) Reb M has gained in popularity over other steviol glycosides as a desired commercial sweetener. The '257 and '273 patents purport to satisfy the need for "simple, efficient, and economical methods for preparing

compositions comprising steviol glycosides." (SUF 2.) The patents share a common specification, claiming priority to May 22, 2012, which states:

> The present invention provides a biocatalytic process for preparing a composition comprising a target steviol glycoside by contacting a starting composition comprising a steviol glycoside substrate with UDP-glucosyltransferase, thereby producing a composition comprising a target steviol glycoside comprising one or more additional glucose units than the [starting] steviol glycoside substrate.

(SUF 3.) The claims of both patents specify that the "target" steviol glycoside to be made is Reb M. (SUF 5-15.) The '273 patent broadly claims making Reb M by converting a specific steviol glycoside—rebaudioside D ("Reb D")—using *any* UDP-glucosyltransferase. (SUF 6.) The '257 patent broadly claims converting *any* steviol glycoside substrate to Reb M using a UDP-glucosyltransferase. (SUF 5.)

Enzymes, such as UDP-glucosyltransferases, are proteins that catalyze (*i.e.*, reduce the activation energy needed for) chemical reactions, thus speeding up the reactions or permitting reactions to go forward that would not otherwise proceed. (SUF 25-26, 32.) Like all proteins, enzymes are composed of chains of amino acids. (SUF 53, 65.) The relationship between an enzyme's amino acid sequence and an enzyme's activity (or functionality) is complex and unpredictable. (SUF 68.) Small changes in the amino acid sequence can result in dramatic changes in activity. (SUF 69.) To determine an enzyme's activity, one must make and test the enzyme. (SUF 78-79.)

The specification defines "biocatalytic process" as "the use of natural catalysts, such as protein enzymes, to perform chemical transformations on organic compounds," where the biocatalyst protein can be "naturally occurring." (SUF 32.) The catalysts claimed in the '257 and '273 patents are UDP-glucosyltransferases, whose natural function is to act as a "common donor of a glucose unit … that they append to an acceptor substrate." (SUF 24-26.) Accordingly, the claims of the patents cover compounds (*e.g.*, Reb M, steviol glycosides, and UDP-glucosyltransferases) and reactions (*e.g.*, biocatalytic processes) that are found in

nature. (SUF 16, 23, 25, 28-30, 32-35.)

In relation to making Reb M, the specification identifies only one suitable UDP-glucosyltransferase enzyme: wild type UGT76G1, which is found naturally in the plant. (SUF 55-57.) The specification includes data for only one conversion process for making Reb M, namely, by using UGT76G1 to convert Reb D to Reb M. (SUF 83.) This is the only working example provided in the specification for producing Reb M. The specification does not provide data or a working example for any other UDP-glucosyltransferase capable of converting Reb D to Reb M. The specification does not provide data or a working example for the conversion of any other steviol glycoside to Reb M. The specification also does not identify which aspects of the amino acid sequence or three-dimensional structure of any UDP-glucosyltransferase would make it a suitable catalyst for making Reb M.

After the priority date of the asserted patents, additional steviol glycosides have been developed and identified. (SUF 91-93.) Reb D4 was unknown as of the priority date of the asserted patents. (SUF 91.) Similarly, after the priority date, additional UDP-glucosyltransferases—including those capable of converting a steviol glycoside to Reb M—have been developed. (SUF 93.) Indeed, the enzyme used to produce the Reb M sold by SweeGen was developed after the priority date by scientists at Conagen. (SUF 92.) Conagen obtained a patent covering this pathway, which coverts Reb D4 to Reb M using a novel fusion enzyme. (SUF 93.)

II. ARGUMENT

Summary judgment should be granted when "the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). As to materiality, "[o]nly disputes over facts that might affect the outcome of the suit under the governing law will properly preclude the entry of summary judgment." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986). "[F]acts must be viewed in the light most favorable to the nonmoving party only if there is a 'genuine' dispute as to those facts." *Scott*

v. Harris, 550 U.S. 372, 380 (2007). "[M]erely conclusory statements or completely insupportable, specious, or conflicting explanations or excuses will not suffice to raise a genuine issue of fact." *Paragon Podiatry Lab., Inc. v. KLM Labs.*, 984 F.2d 1182, 1190 (Fed. Cir. 1993).

A. The claims are invalid under 35 U.S.C. § 101 as patent ineligible.

Whether claims are invalid under § 101 is a question of law. *Essociate, Inc. v. Clickbooth.com,* LLC, No. SACV 13-1886, 2015 WL 1428919, at *3 (C.D. Cal. Feb. 11, 2015) (Selna, J.), *aff'd*, 641 F. App'x 1006 (Fed. Cir. 2016) (citing *In re Comiskey*, 554 F.3d 967, 975 (Fed. Cir. 2009)). Under § 101, an invention is patent-eligible if it claims a new and useful process, machine, manufacture, or composition of matter. "However, § 101 has a longstanding, 'important implicit exception: [l]aws of nature, natural phenomena, and abstract ideas are not patentable.'" *Id.* (citing *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 573 U.S. 208, 211 (2014)). The Supreme Court has distinguished patents that claim "'buildin[g] block[s]' of human ingenuity, which are ineligible for patent protection, from those that integrate the building blocks into something more." *Alice*, 576 U.S. at 211. These exceptions ensure that patent law does not "inhibit further discovery by improperly tying up the future use of laws of nature." *Mayo Collaborative Servs. v. Prometheus Labs., Inc.* 566 U.S. 66, 85 (2012).

The "Supreme Court has set forth a two-step 'framework for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent eligible applications of those concepts.'" *Essociate*, Dkt. 51, at 5 (*quoting Alice*, 576 U.S. at 217). First, "[the Court must] determine whether the claims at issue are directed to one of those patent-ineligible concepts." *Id.* If so, then the second step requires the Court to search for an inventive concept by considering the "elements of each claim both individually and 'as an ordered combination' to determine whether the additional elements 'transform the nature of the claim' into a patent-eligible application." *Id.* Adding only what was "well-

understood, routine, conventional activity previously engaged in by scientists in the field" does not "transform an unpatentable law of nature into a patent-eligible application of such a law." *Mayo*, 566 U.S. at 69, 72.

1. The '257 patent claims are not patent eligible.

a. *Alice* Step One: the claims of the '257 patent are directed to patent-ineligible natural phenomena.

The '257 patent contains seven claims, of which claim 1 is independent:

> 1. A method for adding at least one glucose unit to a steviol glycoside substrate to provide a target steviol glycoside, comprising contacting the steviol glycoside substrate with a recombinant biocatalyst protein enzyme comprising UDP-glucosyltransferase, wherein the target steviol glycoside is Rebaudioside X.

Claim 1 is directed to a process for making Reb M (a natural compound) by converting a steviol glycoside substrate (another natural compound) using a UDP-glucosyltransferase (a naturally occurring enzyme), thus claiming a process that occurs naturally in the stevia plant. (SUF 16, 23, 25, 28-30, 32-35.) Claim 1 does not limit the environment of the claimed process to any non-natural or laboratory setting.

The '257 patent defines the claimed "biocatalytic process" as "the use of natural catalysts, such as protein enzymes, to perform chemical transformations on organic compounds." (SUF 32). The patent recognizes that all the components of the claimed biocatalytic process, (*e.g.*, steviol substrates, target Reb M, and UDP-glucosyltransferase) are also found in nature. (SUF 33-35.) An inventor named on the '257 patent (Dr. Prakash) and PureCircle's expert (Dr. Bollinger) both confirmed that the claimed UDP-glucosyltransferase can occur naturally in the plant. (SUF 35.)

Nor can there be any dispute that the biocatalytic conversion reaction claimed in the '257 patent—converting a steviol glycoside to Reb M using UDP-glucosyltransferase—is the same process that occurs in nature. The specification describes UDP-glucosyltransferases as performing the function of "[a]dding at

least one glucose unit to the steviol glycoside substrate," which undisputedly is a natural process in the stevia plant. (SUF 34.) The claims recite that same step in which "at least one glucose unit" is added to a "steviol glycoside substrate to provide a target steviol glycoside." Enzymes that exist in nature are referred to as "wild-type" enzymes; one particular UDP-glucosyltransferase that exists in nature is UGT76G1. (SUF 28-29.) PureCircle's expert ,Dr. Bollinger, concedes that [redacted] (SUF 40.)

Claim 1 is directed to a natural phenomenon: the natural function of a UDP-glucosyltransferase that exists in nature to add glucose units to a steviol glycoside to produce Reb M—exactly what happens inside the stevia plant. Accordingly, claim 1 of the '257 patent satisfies step one of the Supreme Court's test.

Claim 2 depends from claim 1 and provides a list of "steviol glycoside substrates" for the conversion to Reb M. (SUF 8.) But there is no dispute that this list includes steviol compounds that exist in nature in the stevia plant (SUF 23.) Claim 2, therefore, is likewise directed entirely to natural phenomena.

Claims 3, 4, and 5 each depend from claim 1 and recite an additional step of "purifying the Rebaudioside X to a purity of greater than about" 80% by weight (claim 3), 90% by weight (claim 4), or 95% by weight (claim 5). (SUF 9.) Claim 6 depends from claim 1 and specifies that "the UDP-glucosyltransferase is expressed in a host microorganism." Claim 7 depends from claim 6 and lists potential host microorganisms. None of these additional limitations alters the fact that these claims are directed to naturally occurring processes. And, as discussed below, none of these additional limitations contains an "inventive step" sufficient to transform the claimed naturally occurring processes into a patent-eligible application.

b. *Alice* Step Two: nothing transforms the nature of the claims into a patent-eligible application.

The idea of using a UDP-glucosyltransferase to convert a steviol glycoside substrate into Reb M by adding a glucose unit is not patent eligible—it is a natural phenomenon that occurs in the stevia plant. Step two of *Alice* therefore asks whether there is anything *else* in the claims that is inventive, as opposed to merely well known, conventional, or routine. "For process claims that encompass natural phenomenon [*sic*], the process steps are the additional features that must be new and useful." *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1377 (Fed. Cir. 2015). The Supreme Court has stated that "conventional or obvious" extra-solution activity "is normally not sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law." *Mayo*, 566 U.S. at 79. The "inventive concept" supplied by the claim elements not drawn to ineligible subject matter must therefore be "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself." *Id.* at 72−73.

PureCircle may argue that additional limitations in the '257 patent salvage the claims under § 101—namely, *recombinant* biocatalyst enzyme (claims 1–7), *purity* percentages for Reb M (claims 3–5), and *host microorganisms* to express the UDP-glucosyltransferase (claims 6–7). But none of these elements supplies an inventive concept that transforms the nature of the claims into a patent-eligible application under *Alice* and *Mayo*. Rather, these elements are themselves natural phenomena or well-understood, routine, and conventional activity. PureCircle may also argue that the claims are limited to ex vivo reactions, in which the conversion reactions occur in, e.g., a recombinant cell. That is not correct. Although the enzyme is made recombinantly, it can be used in any environment (including in a stevia plant). More fundamentally, merely replicating natural processes ex vivo would not satisfy Alice step two because the claims would still be directed to a natural process without any non-routine or non-conventional redeeming elements.

Recombinant and host microorganism. Neither the "recombinant" aspect nor the limitations that the recombinant enzyme be "expressed in a host

microorganism" impart patentability. These limitations merely limit the source of the UDP-glucosyltransferase enzyme but specify nothing regarding the *structure* or *function* of the enzyme produced, which can be identical to the wild type (as embodied in the only example provided in the specification) nor any non-natural role the enzyme plays in the claimed process. (SUF 55-56.) Techniques for making proteins, including UDP-glucosyltransferases, in a host microorganism were well understood, routine, and conventional before 2012. (SUF 47.)

The claim term "recombinant biocatalyst protein enzyme" does not place any structural or functional limitations upon the enzyme; therefore, the claimed enzyme can be structurally and functionally identical to the naturally occurring enzyme. (SUF 57.) PureCircle's expert, Dr. Bollinger, conceded that recombinant enzymes expressed in a host microorganism can be identical to their natural counterparts. (SUF 57.) The Court construed "recombinant biocatalyst protein enzyme" to mean "[a] protein enzyme made from a gene that has been cloned and introduced into an expression system." Dkt. 143 at 3. Therefore, a recombinant UDP-glucosyltransferase can have an amino acid sequence identical to that of the naturally occurring UDP-glucosyltransferase and be identical structurally and functionally to naturally occurring UDP-glucosyltransferase. The '257 patent describes recombinant UDP-glucosyltransferases UGT76G1 and UGT91D2 having sequences identical to their natural counterparts in the stevia plant. (SUF 57-58.) Thus, although the "recombinant biocatalyst protein enzyme" is produced in an expression system (*e.g.*, a host microorganism), the claims allow the enzyme to be *used* in *any* environment to make the target steviol glycoside.

It is black-letter law that a man-made component identical in function and structure to its natural counterpart does not overcome ineligibility under § 101. For example, in *Roche Molecular Systems, Inc. v. CEPHEID*, the Federal Circuit affirmed a district court's entry of summary judgment of invalidity of patent claims directed to methods for detecting tuberculosis because the compounds used in the

claimed methods were structurally indistinguishable from and functioned like their natural counterparts. 905 F.3d 1363, 1371 (Fed. Cir. 2018). The claims in *Roche* involved extracting DNA from a biological sample taken from a patient and then amplifying it via polymerase chain reaction using a man-made nucleotide sequence (a "primer") that could bind to the signature nucleotides in a gene unique to the tuberculosis bacteria. *Id*. Because the claimed man-made primer used the same nucleotide sequence as the naturally occurring primer, the Federal Circuit found that the man-made primers and their natural counterparts performed the same function. *Id.* at 1373. Here, too, the claimed recombinant enzyme can have the identical structure and function as its natural counterpart in the plant. (SUF 53-54.)

Similarly, in *Athena Diagnostics, Inc. v. Mayo Collaborative Services, LLC*, the Federal Circuit affirmed a holding that method claims were directed to a natural law despite the patentee's contention that the claims were "directed to a new laboratory technique that makes use of man-made molecules." 915 F.3d 743, 750 (Fed. Cir. 2019). Before the patentee's discovery, there were no disclosed methods to detect these naturally occurring antibodies. But because the natural phenomenon "exist[ed] in nature apart from any human action," the claims failed *Alice* step one, and because the man-made molecules and laboratory techniques were only routine, conventional, and well known, the claims failed *Alice* step two. *Id.* at 753–54.

Additionally, the Federal Circuit in *Biogen MA Inc. v. EMD Serono, Inc.*, held that a "recombinant" protein is not patentably distinct from its naturally occurring counterpart. 976 F.3d 1326, 1332 (Fed. Cir. 2020). Invoking the "longstanding rule that an old product is not patentable even if it is made by a new process," the Federal Circuit held that where the amino acid sequences for both the recombinant and naturally occurring protein were identical, "the recombinant origin of the recited composition cannot alone confer novelty on that composition if the product itself is identical to the prior art non-recombinant product." *Id.* at

1332−33 (internal citations and quotations omitted). The Federal Circuit also determined that the district court had "erred in considering the advantages of the recombinant process—the new capability of manufacturing sufficient quantity of [the polypeptide] through recombinant technology—as a reason not to" compare the structural and functional similarities with the native counterpart. *Id.* at 1334. Here, the only example in the specification provides identical amino acid sequences for both the recombinant and the naturally occurring UDP-glucosyltransferase enzymes, and claims them for the same steviol glycoside reactions, without any difference in identity or function.

Regarding the "host microorganism" limitations of claims 6–7, PureCircle's expert admits that it is "commonplace to apply recombinant DNA technology to program preferred 'host' organisms (such as the bacterium *Escherichia coli* or the yeast *Pichia pastoris*) to produce enzymes that might either be difficult to extract and purify from their natural sources or not exist at all in nature." (SUF 59.). Accordingly, such activity cannot add an inventive concept to claims that are otherwise directed to the natural process of making Reb M with a UDP-glucosyltransferase found in nature. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 591 (2013) ("[Myriad] found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention."); *Roche,* 905 F.3d at 1366.

Purity limitations. The generic purity limitations for Reb M in claims 3–5 do not impart patentability. These claims do not recite any specific manner of purification, nor do they recite any alterations in the conversion of the steviol glycoside substrate to Reb M with UDP-glucosyltransferase recited in claim 1 to achieve the purity thresholds. (SUF 60.) Indeed, the specification expressly states that, to reach a given purity, "[t]he target steviol glycoside can be separated by any suitable method, such as, for example, crystallization, separation by membranes, centrifugation, extraction, chromatographic separation or a combination of such

methods." (SUF 62). All of the "suitable methods" are routine, conventional, and well known, as the specification admits. (SUF 60-62.) Dr. Prakash, a named inventor, testified that a purity threshold of 95% by weight is common for sweeteners. (SUF 64 ([redacted] ").) Appending such routine, conventional post-reaction purification steps to a natural phenomenon does not supply an inventive concept. *See Ariosa*, 788 F.3d at 1378 (holding human action of amplifying cffDNA is not an inventive concept because that technique was well understood, conventional, and routine); *see also Myriad*, 569 U.S. at 591 (explaining that the human action of separating a gene from surrounding genetic material "is not an act of invention.").

2. The '273 patent claims are not patent eligible for substantially the same reasons as the '257 patent.

The '257 and '273 patents issued from the same parent application and share the same specification. The '273 patent has 14 claims; claim 1 is independent:

> 1. A method for making Rebaudioside X comprising a step of converting Rebaudioside D to Rebaudioside X using a UDP-glucosyltransferase, wherein the conversion of Rebaudioside D to Rebaudioside X is at least about 50% complete.

(SUF 1, 6.) Claim 1 of the '273 patent resembles claim 1 of the '257 patent except that it: (1) specifies that the "steviol glycoside substrate" is "Reb D"; (2) does not limit the UDP-glucosyltransferase to recombinantly made forms; and (3) recites that conversion from Reb D to Reb M is "at least 50% complete." (SUF 5-4.)

Despite these differences, and for the reasons discussed above with respect to the '257 patent, claim 1 of the '273 patent is directed to the same natural phenomenon, satisfying *Alice* step one. The first two differences listed above are immaterial to the § 101 inquiry because the specification admits that both Reb D and the UDP-glycosyltransferase UGT76G1 exist naturally in the stevia plant. (SUF 23.) Moreover, Dr. Bollinger admits, consistent with the literature, that Reb D will be converted into Reb M in the presence of UGT76G1. (SUF 35.)

The third difference—that the conversion of Reb D to Reb M is at least

about 50% complete—does not alter the focus of the claims, which remains on a process that occurs in nature. The claims broadly encompass conversions in any environment, including within the stevia plant, where both Reb D and the UDP-glucosyltransferase UGT76G1 exist naturally. (SUF 35.) Moreover, Dr. Bollinger admits that the wild-type form of UGT76G1 is highly efficient at converting Reb D to Reb M and will do so at up to 100% completion. (SUF 38.) Dr. Bollinger further testified that the degree of conversion simply depends on whether there is enough enzyme present to convert a given amount of substrate to Reb M. (SUF 38-40.) This, even under Dr. Bollinger's definition, the claims broadly cover the conversion of *any* amount of Reb D, including trace amounts, to Reb M over time. This unbounded scope reads on natural processes where some amount of Reb D present in the plant will be converted to Reb M over time based on the presence of UGT76G1. Indeed, PureCircle drafted these claims so broadly that, on their face, they literally encompass reacting a *single* Reb D molecule with a UDP-glucosyltransferase to make a *single* Reb M molecule, and Dr. Bollinger admits this. (SUF 116.) In that scenario, the conversion is 100% complete.

Claim 2 of the '273 patent recites that the enzyme comprises *any* UDP-glucosyltransferase capable of adding at least one glucose unit to Reb D to form Reb M, which occurs in nature. (SUF 13.) Claim 3 recites that a glucose molecule is added to a C-19 position of Reb D, which occurs in nature (because it is how to make Reb M from Reb D). (SUF 14.) Claims 4–6 recite purifying Reb M to a concentration of 80% (claim 4), 90% (claim 5), or 95% (claim 6) by weight, which are the same purity limitation as in claims 3–5 of the '257 patent discussed above. Claims 7–11 recite that the conversion from Reb D to Reb M is at least about 60% (claim 7), 70% (claim 8), 80% (claim 9), 90% (claim 10), or 95% (claim 11) complete. (SUF 43.) Claim 12 (like claim 6 of the '257 patent) recites that the UDP-glycosyltransferase is expressed in a host microorganism. Claim 13 (like claim 7 of the '257 patent) lists host microorganisms. Claim 14 specifies the UDP-

glucosyltransferase comprises UGT76G1, which is found in nature. (SUF 15.)

The parties do not dispute that claims 1–14 of the '273 patent are directed to making Reb M (which exists naturally in the stevia plant) from Reb D (which exists naturally in the stevia plant) using a UDP-glucosyltransferase (including UGT76G1, which exists naturally in the stevia plant) (SUF 6.) Nor is there any dispute that the conversion of Reb D to Reb M by UGT76G1 can occur efficiently in nature. (SUF 38.) No claim in the '273 patent specifies that the conversion reaction must occur in a non-naturally occurring environment.

Given their high level of generality and overall character, each claim of the '273 patent is directed to a natural phenomenon for the same reasons as the claims of the '257 patent discussed above. The specification admits that the generic step of purifying the product can be accomplished using well-known, conventional, and routine techniques. (SUF 61-62.) Accordingly, these steps fail to transform the recited natural process into a patent-eligible application of that natural process.

Conversion limitations. The claims of the '273 patent require that the conversion of Reb D to Reb M is at least 50% complete, with claims 7–11 reciting completion percentages. (SUF 43.) But these claims do not specify any starting amount, any end amount, or any reaction time. (SUF 44.) Nor do they recite any steps to achieve these specific conversion thresholds. (SUF 44.) These conversion limitations, therefore, reflect nothing more than the extent to which the claimed reaction has progressed. (SUF 45.) And to the extent the reaction is more or less complete, Dr. Bollinger admits that any amount of Reb D would be converted to Reb M in the presence of a suitable UDP-glucosyltransferase, such as UGT76G1, over time. (SUF 38-40, 46). He further admits that wild type UGT76G1, as it exists in nature, is particularly efficient at converting Reb D to Reb M. (SUF 38.) Therefore, conversion rates above 50% and approaching 100% can occur in nature, and each such limitation for conversion is simply descriptive of those phenomena.

Simply claiming that a natural phenomenon has progressed to a certain

extent is insufficient under the Federal Circuit's precedent that eligibility requires "more than simply stat[ing] the law of nature while adding the words 'apply it.'" *Ariosa*, 788 F.3d at 1377 (*quoting Mayo*, 566 U.S. at 72). Moreover, applying a natural law in a laboratory setting, using only "conventional or known laboratory techniques," including "*in vitro* methods" (*i.e.*, performing methods "outside of the main organism"), is insufficient to transform it into patent-eligible subject matter. *Genetic Veterinary Scis., Inc. v. LABOKLIN GmbH & Co. KG*, 933 F.3d 1302, 1319 (Fed. Cir. 2019) (explaining that "well-understood, routine, conventional activities … claimed … at a high level of generality" do not recite an inventive concept). In this case, the specification describes nothing new or inventive relating to performing bioconversion reactions, but instead confirms that doing so involves well-known, conventional, and routine techniques that were "already engaged in by the scientific community" before 2012. (SUF 60-62.) *Mayo*, 566 U.S. at 79–80.

Roche, again, is instructive. There, the claims covered testing that was "both faster and more accurate," however, the Federal Circuit held the claims invalid because the compounds used in the claimed method were indistinguishable from and acted with the same function as their natural counterparts. 905 F.3d at 1366. The present case is no different. The '273 claims cover compounds—Reb D, Reb M, the UDP-glucosyltransferase UGT76G1—that have the same structure and function as their natural counterparts. Differences in the speed or efficiency of the reaction owing to the use of well-known, conventional, and routine laboratory practice do not transform the natural law into a patent-eligible application.

Similarly, in *Biogen MA*, the Federal Circuit held that the district court "erred in considering the advantages of the [claimed process]—the new capability of manufacturing sufficient quantities of [the protein] through [the claimed technology]"—in trying to distinguish the claimed protein from an identical one found in nature. 976 F.3d at 1334–35. That is, the claimed process's ability to produce more quantities of the desired product using the human-made protein

recited in the claim did not distinguish that product from its natural counterpart.

The same holds true here. The conversion limitations do not recite *any* method of increasing yield Reb M, let alone a *new* or *useful* method. Instead, they merely describe what occurs when any or some undetermined amount of Reb D is converted to Reb M in the presence of a UDP-glucosyltransferase—a process that occurs efficiently in nature and can be performed *in vitro* using only conventional, well-known, and routine techniques. The specification concedes this point by limiting its description of such *in vitro* conditions to a generic discussion of a suitable "reaction medium," various potential temperatures, and timeframes for the reaction ranging from 1 hour to 7 days. (SUF 49, 62.) In the only relevant working example of this conversion in the specification (Example 6), 180 µL of wild type UGT76G1 is combined in a reaction medium consisting of commercially available media components and buffers to catalyze conversion of 0.5 mM of Reb D into Reb M to "80% conversion" after 120 hours. (SUF 48-49.) The fact that the patent broadly claims conversion rates up to 100%, even though the highest rate demonstrated in the specification is limited to 80%, indicates that achieving higher rates must have been within the ken of a skilled artisan, for the inventors plainly thought no further instructions on how to achieve rates above 80% were needed.

Purity limitations (claims 4–6). Like the '257 patent, the '273 patent does not claim any particular manner of purification. (SUF 60.) Nor does it claim alterations in the conversion of Reb D to Reb M with UDP-glucosyltransferase to achieve the claimed purity thresholds. (SUF 60.) In fact, the specification and admissions by a named inventor indicate that the purity steps are routine and conventional steps claimed at a high level of generality. *See supra* at 13–14. Such elements are insufficient to supply an inventive concept. *See Ariosa*, 788 F.3d at 1378 (finding process step that increased yield of paternal DNA through routine, conventional amplification technique did not confer inventive concept).

Host organism (claims 12 and 13). As with claims 6 and 7 of the '257

patent, PureCircle admits that the use of a host organism to express a protein is "commonplace." *See supra* at 9–13. By definition, therefore, this represents a well-known, conventional, and routine step that is insufficient to supply an inventive concept. *Ariosa*, 788 F.3d at 1378 (finding amplification of DNA extracted from blood to be a routine and conventional step that did not confer inventive concept).

UGT76G1 (claim 14). Claim 14 recites "the UDP-glucosyltransferase comprises UGT76G1." There is no dispute that UGT76G1 is an enzyme that can occur naturally in the stevia plant. *See supra* at 7, 10, 16. There also is no dispute that wild type UGT76G1 can convert Reb D to Reb M, as claimed. (SUF 35-36.)

* * * * *

Mayo warned "against upholding patents that claim processes that too broadly pre-empt the use of a natural law." 566 U.S. at 72. The claims of the '257 and '273 patents are so broad that they monopolize a natural process (biocatalytic conversion) to make a naturally occurring compound (Reb M) using naturally occurring enzymes (including UGT76G1). Patent law should "not inhibit further discovery by improperly tying up the future use of laws of nature." *Id.* at 85.

B. <u>The claims are invalid for lack of written description under § 112.</u>

"To fulfill the written description requirement, a patent owner 'must 'convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention,' and demonstrate that by disclosure in the specification of the patent.'" *Idenix Pharms., LLC v. Gilead Sciences Inc.*, 941 F.3d 1149, 1163 (Fed. Cir. 2019). The specification must adequately describe the full scope of what is claimed. *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1353−54 (Fed. Cir. 2010) (en banc). "Requiring a written description of the invention limits patent protection to those who actually perform the difficult work of 'invention'—that is, conceive of the complete and final invention with all its claimed limitations—and disclose the fruits of that effort to the public." *Id.*

Broad and functionally defined genus claims—such as those at issue here—

"can be inherently vulnerable to invalidity challenge for lack of written description support, especially in technology fields that are highly unpredictable, where it is difficult to establish a correlation between structure and function for the whole genus or to predict what would be covered by the functionally claimed genus." *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1301 (Fed. Cir. 2014). Further, "[s]ome factors to consider when evaluating the adequacy of the disclosure include 'the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue.'" *Juno Therapeutics, Inc. v. Kite Pharma, Inc.*, 10 F.4th 1330, 1335 (Fed. Cir. 2021) (quoting *Ariad*, 598 F.3d at 1351). As shown below, the patents' shared specification fails to provide written description for the full scope of the claimed genus of UDP-glucosyltransferases.

1. The claims encompass a limitless number of enzymes, including UDP-glucosyltransferases yet to be discovered.

All the claims of the '257 and '273 patents broadly cover a genus of enzymes (UDP-glucosyltransferases) defined by a function (the ability to transfer a glucose unit). The stipulated construction of "UDP-glucosyltransferase" is "[a] type of enzyme that is capable of transferring a glucose unit from a [UDP] molecule to a steviol glycoside molecule." Dkt. 143, 2-3. PureCircle's expert, Dr. Bollinger, admits that the term "UDP-glucosyltransferase" as used in the patent encompasses [redacted]" (SUF 99.) That definition covers not just naturally occurring UDP-glucosyltransferases, but "any" UDP-glucosyltransferase mutant, fusion, and UDP-glucosyltransferase known or discovered *after* the patents' May 22, 2012 filing date. (SUF 94-102.)

A "mutant" generally refers to a variant form of an enzyme that results from mutagenesis, and can result from natural mutation or mutations introduced through engineering. (SUF 72-73.) A "fusion" refers to an enzyme that, in addition to the UDP-glucosyltransferase portion, contains another protein domain. (SUF 97.)

Dr. Bollinger admits that the defining feature of a UDP-glucosyltransferase, as used in the patents, is based on *function* (*i.e.*, any enzyme that "is capable of transferring a glucose unit"), not on any structure. (SUF 99, 100–103.) Given this definition, a conservative estimate of the number of enzymes covered by the claims exceeds 1.1 x 10^{12} candidates (one thousand billion). (SUF 107, 108.) The claims could thus cover a "limitless number" of compounds. *Juno*, 10 F.4th at 1337.

Claims 2, 3, and 14 are the only claims of the '273 patent that put any type of limitation on what qualifies as a UDP-glucosyltransferase, yet each still broadly includes any mutant, fusion, or form of the recited enzyme yet to be discovered.

Claim 2 of the '273 patent recites "wherein the UDP-glucosyltransferase comprises any UDP-glucosyltransferase capable of adding at least one glucose unit to Rebaudioside D to form Rebaudioside X." Rather than add specificity, claim 2 merely confirms that "any" UDP-glucosyltransferase is included and that the UDP-glucosyltransferase is defined entirely based on its function and not its structure.

Claim 3 of the '273 patents recites "wherein the UDP-glucosyltransferase is capable of adding a glucose unit to a C-19 position of Rebaudioside D" which adds where the glucose can be added, but is still a broad functional definition covering a limitless number of enzymes, known and unknown, including mutants and fusions.

Claim 14 of the '273 patent recites "wherein the UDP-glucosyltransferase comprises UGT76G1," however, this *still* does not restrict the claimed coverage to a reasonable number of enzymes. Rather than limit the scope of claim 14 to the wild-type sequence of UGT76G1 identified in the specification, claim 14 uses the open ended phrase "the UDP-glucosyltransferase *comprises* …." (SUF 88, 98, 103, 104; emphasis added.) Dr. Bollinger admits that, owing to this breadth, "[redacted]" (SUF 98.)

Thus, claim 14, despite reciting "UGT76G1," still encompasses a limitless number of enzymes—including all mutants, derivatives, or fusions of UGT76G1.

Turning to the '257 patent, the claims recite making Reb M using "a recombinant biocatalyst protein enzyme comprising UDP-glucosyltransferase." (SUF 5.) This, too, broadly encompasses all mutants and fusions of recombinant UDP-glucosyltransferases, including those yet to be discovered. The stipulated construction of "recombinant" is that the enzyme be "made from a gene that has been cloned and introduced into an expression system." Dkt. 143, 3. This does not limit what the enzyme is, but rather specifies how the enzyme is *made*. (SUF 105.) Therefore, as with the '273 patent, the claims of the '257 patent define the genus functionally, in terms of an enzyme's ability to add glucose to a steviol glycoside.

Using broad functional boundaries, the claims thus encompass a limitless number UDP-glucosyltransferase mutants and fusions, both known and yet to be discovered. The written description requirement is intended to guard against such overreaching. *Idenix*, 941 F.3d at 1164-65 ("The written description requirement specifically defends against such attempts to 'cover any compound later actually invented and determined to fall within the claim's functional boundaries.'").

2. The specification does not describe a representative number of species or identify any common structural features.

The breadth of the claims contrasts sharply with the limited disclosure in the specification. When a genus is claimed, the specification must provide description of "either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one of skill in the art can visualize or recognize the members of the genus." *Ariad*, 598 F.3d at 1350 (citations omitted); *Juno*, 10 F.4th at 1335; *Idenix*, 941 F.3d at 1164.

Far from providing a representative number of species for this massive genus, which includes all mutants and fusions, the specification identifies *only one* enzyme as suitable for making Reb M from Reb D: wild type UGT76G1. (SUF 83−86.) It is identified as useful for converting Reb D to Reb M. And as for experimental data, the specification includes only one relevant example: the conversion of Reb D to Reb M using *in-vitro*-produced wild type UGT76G1. (SUF

48, 49, 83.) The specification does not describe the concept of mutants or fusions, let alone provide any specific examples. It does not describe what about the amino acid sequence or three-dimensional structure of UGT76G1 makes it suitable for making Reb M from Reb D. And it does not identify features that make other UDP-glucosyltransferases capable of performing this function, or why. Indeed, to the extent the specification says anything about the relationship between sequence similarity and enzymatic activity, it indicates that these things are *not* correlated. The specification states that another enzyme, UGT91D2e shares a ">95% identity with UGT91D11 … and >99% identity" with UGT91D2, which is identified as an enzyme suitable for producing Reb D from Reb A. (SUF 110, 111.). Yet the specification does not identify UGT91D2e or UGT91D11 as suitable for producing Reb D from Reb A. Therefore—per the specification—having a similar (>99% identical) amino acid sequence to a UDP-glucosyltransferase that is capable of performing a function does not mean that a UDP-glucosyltransferase having a nearly identical amino acid sequence will perform the same function.

In sum, there is no description of a representative number of species. There is no guidance as to what other species would provide the same result. And there is no description of what structural features are common to the functional genus.

Where, as here, the claims cover a broad and functionally defined genus and the specification merely "provide[s] lists or examples of supposedly effective [UDP-glucosyltransferases], but do[es] not explain what makes them effective, or why . . . , [a skilled artisan] is deprived of any meaningful guidance into what [UDP-glucosyltransferases] beyond the examples and formulas, if any, would provide the same result." *Idenix*, 941 F.3d at 1164. In that case, "listed examples and formulas cannot provide adequate written description support for undisclosed [UDP-glucosyltransferases] that also happen[] to [satisfy the functional term]." *Id.*

3. A skilled artisan would have had to discover, make, and test countless enzymes to identify what the claims cover.

Acknowledging that the claims encompass a countless variety of mutants and fusions, none of which are described in the specification, Dr. Bollinger asserts that a skilled artisan could have employed computer modeling, high-throughput screening, and robotics to *discover* candidates and *test* them to determine whether they are capable of performing the claimed reactions. (SUF 66-68, 112.) Whatever the capabilities of these tools, there is no dispute that such discovery and research are a prerequisite to understanding what the claims cover. A written description that necessitates such a search is inadequate under § 112 because it evinces a lack of possession. *Ariad*, 598 F.3d at 1356 ("[A] vague functional description and an invitation for further research does not constitute written disclosure of a specific [compound].") (citations omitted); *id.* at 1353 ("[A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

Indeed, developing a UDP-glucosyltransferase capable of making Reb M—whether a mutant or fusion or both—may be inventive in its own right, and "[t]he written description requirement specifically defends against such attempts to 'cover any compound later actually invented and determined to fall within the claim's functional boundaries.'" *Idenix*, 941 F.3d at 1164−65. In this case, PureCircle is attempting to read its patent on a novel fusion enzyme invented by others. Indeed, scientists at Conagen received their own patent covering the pathway used to make SweeGen's Reb M product, which relies on a different steviol glycoside substrate (Reb D4) and a novel fusion enzyme. (SUF 92-93.) Yet the PureCircle inventors were unaware of Reb D4 or this enzyme. (SUF 91.) This is, thus, a textbook case of a patentee using vague functional claiming to cover anything later actually invented.

4. No UDP-glucosyltransferase structures were known and an enzyme's activity is not predictable based on its sequence.

Dr. Bollinger admits that the physical structure of an enzyme must be experimentally determined using methods such as "[redacted]." (SUF 74.) He further admits that "no experimentally

determined structure of a UDP-glucosyltransferase was known in 2012." (SUF 82.) Therefore, admittedly, no UDP-glucosyltransferase structures were available as of the filing date to establish a correlation between enzyme structure and function.

Rather, Dr. Bollinger points to the availability of computer software that a skilled artisan could use to make *models* of predicted enzyme structure based on sequence homology. (SUF 80.) Importantly, these are not real experimentally determined structures, but computer simulations generated based on amino acid sequences. (SUF 80.) Dr. Bollinger concedes that such modeling is insufficient to determine the activity of an enzyme in the real world and must always be coupled with experimental screening. (SUF 66-68.) Screening means making and testing the enzyme in a laboratory in order to determine whether, in reality, the enzyme catalyzes a given reaction. (SUF 68.) Named inventor Dr. Indra Prakash agreed that one cannot predict how a given enzyme will function [redacted]" stating one would have to [redacted]." (SUF 113, 114, 68.) Named inventor Dr. Avetik Markosyan likewise confirmed that "[redacted]" (SUF 75.) Dr. Prakash testified that he had tried to use different UDP-glucosyltransferases to catalyze production of Reb M but was not consistently successful. (SUF 115.) ("[redacted]") This demonstrates that not even the inventors knew which other enzymes would be suitable for performing the claimed reactions.

Testing is also required because similarity between amino acid sequences cannot alone predict enzyme activity. Small changes in the amino acid sequence of a UDP-glucosyltransferase can make a significant difference in its activity. For example, a single point mutation in the UDP-glucosyltransferase UGT76E4 results in expanded activity in terms of its ability to catalyze different reactions involving different substrates. (SUF 69.) This gain of function would not be predictable from the change in a *single amino acid* on this 452-amino-acid enzyme. (SUF 69.) And

the opposite is true: UDP-glucosyltransferases having very little sequence identity can catalyze the same reactions. For example, the enzyme EUGT11 produced in the plant species *Oryza sativa* shares only 39.9% sequence identity with UGT91D2 produced in *Stevia rebaudiana*. (SUF 70.). Yet both are capable of catalyzing the same glucose transfers. (SUF 70.) Simply put, amino acid sequence and modeling cannot determine UDP-glucosyltransferase activity. Testing is always required.

5. The prior art confirms that the amino acid sequence of a UDP-glucosyltransferase does not predict its activity.

As of the May 22, 2012 filing date, only 12 UDP-glucosyltransferases had been identified and only four had been proven capable of adding glucose to steviol glycosides. (SUF 71.) Apart from those four examples, the skilled artisan would have had no data to inform his or her understanding of this vast and diverse genus. Admittedly, there was not a single structure of a UDP-glucosyltransferase in the art, and thus no structural features to correlate to the claimed function. (SUF 81.)

Moreover, the prior-art Richman 2005 paper shows that only *one quarter* of the enzymes chosen for screening (3 of 12) based a consensus sequence associated with binding a UDP-sugar proved to have relevant enzymatic activity. (SUF 71.) Thus, the prior art showed that the vast majority of UDP-glucosyltransferases with even this consensus sequence did not correlate in terms of function. (SUF 71.)

* * * * *

Given the lack of information in the specification to inform skilled artisans which UDP-glucosyltransferases would satisfy the broad and functionally defined genus of enzymes claimed, the specification fails to convey that the inventors had possession of the full scope of the claims. The claims thus amount to nothing more than an impermissible "invitation for further research." *Ariad*, 598 F.3d at 1356.

Others have taken on that further research, discovering—and patenting—a novel pathway and UDP-glucosyltransferase fusion enzyme, which are used to make SweeGen's Reb M product. Neither was known to the named inventors. The claims fail to satisfy the written description requirement, which "defends against

such attempts to 'cover any compound later actually invented and determined to fall within the claim's functional boundaries.'" *Idenix*, 941 F.3d at 1164-65.

C. The claims are invalid for lack of enablement under § 112.

Enablement considers whether "the specification teach[es] those in the art to make and use the invention without undue experimentation." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). It must "enable an ordinarily skilled artisan to make and use the entire scope of the claimed invention at the time of filing." *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012). Whether experimentation is undue considers factors, including: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *Wands*, 858 F.2d at 737. As shown below, the specification is not enabling.

1. The quantity of experimentation needed to discover all of the UDP-glucosyltransferases being claimed is enormous.

As Dr. Bollinger and named inventor Dr. Prakash have admitted, a skilled artisan would have had to discover and analyze millions of candidate enzymes, "a large fraction" of which would need to be made and screened to determine whether each is—in fact—capable of performing the claimed function. (SUF 73.) This is undue experimentation. *Idenix*, 941 F.3d at 1163 (noting: "[T]here were at least many, many thousands of candidate compounds, many of which would require synthesis and each of which would require screening. That constitutes undue experimentation."); *see also Wyeth & Cordis Corp. v. Abbott Lab'ys*, 720 F.3d 1380, 1385–86 (Fed. Cir. 2013) (holding claims invalid for lack of enablement where there was no dispute "practicing the full scope of the claims would require synthesizing and screening each of at least tens of thousands of compounds").

In this case, the claims cover a limitless number of mutants, fusions, and UDP-glucosyltransferases yet to be discovered. There is no dispute that enzyme

function cannot be predicted based on sequence alone. (SUF 66-68.) And there is no dispute that testing is required to determine which of the millions of candidate enzymes possess the claimed functionality. (SUF 66-68.) Rather that dispute these facts, Dr. Bollinger tries to minimize the experimentation as "routine." (SUF 112.) But where "practicing the full scope of the claims would have required excessive experimentation, *even if routine* …" there is a lack of enablement. *Wyeth*, 720 F.3d at 1384 (emphasis added); *see also Idenix*, 941 F.3d at 1163; *Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1087 (Fed. Cir. 2021). Thus, even assuming for the sake of argument that computer modeling, high-throughput screening, and robotic automation were somehow regarded as routine in this field, the need for a skilled artisan to perform such an elaborate and excessive analysis is undue experimentation.

Moreover, in practice, modeling followed by experimentation is an iterative process, one not even Dr. Bollinger would agree can be described as "easy." (SUF 77.) As Dr. Gervay Hague testified, using modeling in combination with screening is "an iterative process between the scientist and the tool," and one that involves trial and error because "if, for example, you made choices, and then … nothing's active … you'll go back to the previous ones that you ruled out." (SUF 78, 80.) As Dr. Prakash, a named inventor, admitted in reference to the use of modeling and screening to discover UDP-glucosyltransferases that function to catalyze specific steviol glycoside reactions: [redacted]" (SUF 79.)

The law is clear that a "specification that requires a POSA to 'engage in an iterative, trial-and-error process to practice the claimed invention' does not provide an enabling disclosure." *Idenix*, 941 F.3d at 1161 (quoting *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010)). That is precisely the case here.

2. There is no direction or guidance in the specification for how to identify members having the claimed function.

As shown above, the specification defines "UDP-glucosyltransferase" in broad functional terms, encompassing "any" UDP-glucosyltransferase, whether a

mutant, fusion, or UDP-glucosyltransferase yet to be discovered, that is "capable" of converting any steviol glycoside substrate (the '257 patent) or Reb D (the '273 patent) to Reb M. *See supra* § III.B.1. But the specification offers no guidance at all about how to identify the members of the vast functionally defined genus. For example, the specification does not explain why the wild-type form of UGT76G1 has this capability, or how to identify other UDP-glucosyltransferases that do. The specification does not even mention mutants or fusions, let alone describe which are capable of performing the claimed reactions. And while Dr. Bollinger asserts that computer modeling, high-throughput screening, and robotic automation could be developed to discover what is covered by the claims, the specification does not mention any of these technologies, let alone offer guidance for how to apply them. Dr. Bollinger also admits that the depictions provided in his report illustrating the three-dimensional structure of UGT76G1 did not exist as of 2012. (SUF 81.)

Without guidance as to how to identify enzymes capable of performing the claimed function, the specification offers, at best, "a starting point, a direction for further research," which is not enabling. *Idenix*, 941 F.3d at 1160 (quoting *ALZA*, 603 F.3d at 941). Thus, the lack of guidance weighs heavily against enablement.

3. The specification has only one relevant working example: using wild type UGT76G1 to convert RebD to RebM.

The specification contains only one relevant working example, which shows conversion of Reb D to Reb M using an *in-vitro*-produced wild-type UGT76G1. *See supra* § III.B.2. One working example using a known UDP-glucosyltransferase is extremely narrow compared to the breadth of the genus, which includes every wild-type, mutant, and fusion of any UDP-glucosyltransferase—out of the 1.1 X 10^{12} candidates—capable of converting any steviol glycoside substrate (the '257 patent) or Reb D (the '273 patent) to Reb M. *See supra* § III.B.2. Where, as here, "working examples are present but are 'very narrow, despite the wide breadth of the claims at issue,' this … weighs against enablement." *Idenix*, 941 F.3d at 1161 (quoting *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362 (Fed. Cir. 1999)).

4. The nature of the invention is complex as it involves the chemical transformation of steviol glycoside substrates.

All the claims recite the use of a UDP-glucosyltransferase for the production of Reb M. The specification describes the technical field as "a biocatalytic process for preparing compositions comprising steviol glycosides." (SUF 4.) Given the nature of the invention, the specification should provide guidance regarding these processes, including which enzymes are capable of catalyzing the reactions. *Idenix*, 941 at 1159; *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997) ("It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention … to constitute adequate enablement.").

5. The prior art was not well-developed: there were only 12 UDP-glucosyltransferases in the prior art and no structures.

As shown above, only 12 UDP-glucosyltransferases had been identified as of the May 22, 2012 patent filing date, and a mere four of those had been shown to have activity in terms of adding glucose units to steviol glycosides. *See supra* § III.B.5. As Dr. Bollinger admits, there were no experimentally determined three-dimensional structures available for any UDP-glucosyltransferase as of 2012. (SUF 82.) Yet the term "UDP-glucosyltransferase," as applied in the patents, includes countless enzymes—including those yet to be discovered. (SUF 72−73, 87−89, 94−108.) The minimal data available about the members of this class as of 2012—including which enzymes were capable of converting steviol glycosides (including Reb D) to Reb M—as well as the potential for significant variation and diversity within the functional class weighs against enablement. *Amgen*, 987 F.3d at 1088.

6. A skilled artisan, regardless of their qualifications, would not be able to predict enzyme activity without testing.

The skilled artisan would have been highly educated yet nevertheless unable to determine *a priori* which of the countless enzymes, aside from the handful that had been characterized, could perform the claimed functions. *See supra* III.B.3−4.

7. Biocatalytic reactions are not predictable absent empirical data characterizing the functionality of a given enzyme.

As Dr. Bollinger and named inventor Dr. Prakash admitted, testing would be necessary in every instance to determine whether an enzyme will have the function used to define the term "UDP-glucosyltransferase" in the patents. (SUF 66-68, 75-79, 112-115); *see supra* § III.B.3−4. Thus, even if models were utilized, it remains undisputed that any prediction made by the model would not suffice to determine enzymatic activity and, therefore, each enzyme would need to be made and tested.

The specification confirms the lack of predictability: sequence similarity to the described embodiments does not dictate suitability for the claimed methods. (SUF 110, 111.) Given the unpredictable nature of enzymatic activity, a skilled artisan could not make and use the full scope of the claims absent extensive and undue experimentation. *See Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1348 (Fed. Cir. 2019) (finding disclosure "insufficient to enable the breadth of the claims … in light of the unpredictability in the art"); *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970) (noting that "[i]n cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability").

8. The breadth of the claims is extreme, functionally covering "any" UDP-glucosyltransferase—known or unknown.

As shown above, all the claims include broad functional limitations. *See supra* § III.B.1. "[T]he use of broad functional claim limitations raises the bar for enablement." *Amgen*, 987 F.3d at 1087; *Idenix*, 941 F.3d at 1156-57 (where "the quantity of experimentation required to determine which [structures] meet [the functional requirements] is very high, [it] favors a finding of non-enablement").

As in *Amgen*, "[t]he functional limitations here are broad, the disclosed examples and guidance are narrow, and no reasonable jury could conclude under these facts that anything but 'substantial time and effort' would be required to reach the full scope of claimed embodiments." *Amgen*, 987 F.3d at 1088.

III. CONCLUSION

The Court should hold all claims of the '257 and '273 patents invalid.

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Respectfully submitted,

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